```
d hist

     (FILE 'HOME' ENTERED AT 12:31:58 ON 05 APR 2001)

     FILE 'EMBASE, MEDLINE, BIOSIS, CAPLUS, USPATFULL' ENTERED AT 12:32:21 ON
     05 APR 2001
L1          12083 S ALPHA-KETOGLUTARATE OR ALPHA-KG
L2           3421 S ALPHA-KETOGLUTARIC ACID
L3         113331 S GLUTAMINE
L4         530638 S AMMONIUM OR AMMONIUM CHLORIDE
L5        4950953 S PROTEIN
L6          27585 S CATABOLIC
L7              0 S L1 AND L2 AND L3 AND L4 AND L5 AND L6
L8            917 S L1 AND L2
L9            138 S L8 AND L3
L10            28 S L9 AND L4
L11            14 S L10 AND L5
L12             0 S L11 AND POSTOPERAT?
L13             1 S L11 AND (OPERATION OR TRAUMA)
L14            12 S L11 AND PY<2000
L15             7 S L9 AND (SEPSIS OR SURGERY OR PROTEIN CATABOLISM)
L16             7 DUP REM L15 (0 DUPLICATES REMOVED)
L17             0 S L16 AND AMMONIUM
L18         77017 S L4 AND (SEPSIS OR SURGERY OR OPERATION OR TRAUMA OR PROTEIN
L19           129 S L18 AND L1
L20            20 S L19 AND L3
L21            16 S L20 AND PY<2000
L22             6 S L21 AND MUSCLE
```

L16 ANSWER 5 OF 7 MEDLINE

TI **Glutamine** and **alpha-ketoglutarate** prevent the decrease in muscle free **glutamine** concentration and influence protein synthesis after total hip replacement.

AB After surgical trauma, protein synthesis, as well as the concentration of free **glutamine** in muscle, decreases. Total parenteral nutrition (TPN) alone does not prevent the decrease of **glutamine** in muscle, but TPN supplemented with **glutamine** or its precursor, **alpha-ketoglutarate**, maintains amino acid concentration in muscle and preserves protein synthesis. The aim of this study was to characterize a human trauma model using patients undergoing total hip replacement, and furthermore to investigate whether **glutamine** or **alpha-ketoglutarate** alone without TPN can prevent the postoperative decrease in muscle free **glutamine**. Metabolically healthy patients undergoing total hip replacement were randomized into three groups. The control group (n = 13) received glucose 2 g/kg body weight (BW) during **surgery** and the first 24 postoperative hours. The **glutamine** group (n = 10) received glucose 2 g/kg BW and **glutamine** 0.28 g/kg BW, and the **alpha-ketoglutarate** group (n = 10) received glucose 2 g/kg BW and **alpha-ketoglutarate** 0.28 g/kg BW. Muscle biopsies were performed before **surgery** and 24 hours postoperatively. Free **glutamine** concentration in muscle decreased from 11.62 +/- 0.67 to 9.80 +/- 0.36 mmol/kg wet weight in the control group (P < .01), whereas it remained unchanged in both the **glutamine** group and **alpha-ketoglutarate** group. Protein synthesis, as reflected by the concentration of total ribosomes, decreased significantly in the control group, but not in **glutamine** and **alpha-ketoglutarate** groups. Polyribosome concentration decreased significantly in both the control and **alpha-ketoglutarate** groups. Total hip replacement can be used as a reproducible trauma model, with characteristic changes in the muscle amino acid. . . .

CT . . . . Tags: Human
- Amino Acids: BL, blood
- Amino Acids: ME, metabolism
- Blood Glucose: ME, metabolism
- C-Peptide: BL, blood
- Glucagon: BL, blood
- **Glutamine: AD, administration & dosage**
- ***Glutamine: ME, metabolism**
- ***Glutamine: TU, therapeutic use**
- *Hip Prosthesis
- Hydrocortisone: BL, blood
- Insulin: BL, blood
- Ketoglutaric Acids: AD, administration & dosage
- *Ketoglutaric Acids: TU, . . .

RN 11061-68-0 (Insulin); **328-50-7 (alpha-ketoglutaric acid)**; 50-23-7 (Hydrocortisone); **56-85-9 (Glutamine)**; 9007-92-5 (Glucagon)

AN 95396256 MEDLINE

DN 95396256

TI **Glutamine** and **alpha-ketoglutarate** prevent the decrease in muscle free **glutamine** concentration and influence protein synthesis after total hip replacement.

AU Blomqvist B I; Hammarqvist F; von der Decken A; Wernerman J

CS Department of Anesthesiology and Intensive Care, Huddinge University Hospital, Sweden.

SO METABOLISM: CLINICAL AND EXPERIMENTAL, (1995 Sep) 44 (9) 1215-22.
Journal code: MUM. ISSN: 0026-0495.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 199512

L16 ANSWER 6 OF 7 MEDLINE
TI **Alpha-ketoglutarate** preserves protein synthesis and free **glutamine** in skeletal muscle after **surgery**.
AB . . . (n = 21) undergoing elective cholecystectomy received postoperative total parenteral nutrition with (n = 9) or without (n = 12) **alpha-ketoglutarate** (AKG) supplementation. Skeletal muscle biopsy specimens were taken before **surgery** and on the third postoperative day. The postoperative decreases in the concentrations of free **glutamine** and basic amino acids seen in the control group were counteracted in the AKG group (p less than 0.05). Muscle. . .

2.6 gm of nitrogen, which was significantly different (p less than 0.05). Administration of AKG, the carbon skeleton corresponding to **glutamine**, produced results similar to those seen when **glutamine** is added to postoperative total parental nutrition. The results suggest that the availability of precursors for **glutamine** synthesis in skeletal muscle is crucial for the degree of muscle **protein catabolism** after surgical trauma.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
*Amino Acids: ME, metabolism
***Glutamine: ME, metabolism**
*Ketoglutaric Acids: PD, pharmacology
Middle Age
*Muscle Proteins: BI, biosynthesis
*Muscles: DE, drug effects
*Muscles: ME, metabolism
Nitrogen:. . .
RN **328-50-7 (alpha-ketoglutaric acid); 56-85-9 (Glutamine)** ; 7727-37-9 (Nitrogen)
AN 91081923 MEDLINE
DN 91081923
TI **Alpha-ketoglutarate** preserves protein synthesis and free **glutamine** in skeletal muscle after **surgery**.
AU Hammarqvist F; Wernerman J; von der Decken A; Vinnars E
CS Department of Surgery, Karolinska Institute, St Goran's Hospital, Stockholm, Sweden.
SO SURGERY, (1991 Jan) 109 (1) 28-36.
Journal code: VC3. ISSN: 0039-6060.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199104

L16 ANSWER 7 OF 7 MEDLINE
TI **Alpha-ketoglutarate** and postoperative muscle catabolism.
AB The hypothesis that muscle **protein catabolism** after trauma is associated with a shortage of **alpha-ketoglutarate**, rather than **glutamine**, was tested. Addition of **alpha-ketoglutarate** to postoperative total parenteral nutrition prevented the decrease in muscle protein synthesis and free **glutamine** that usually occurs after **surgery**. **alpha-ketoglutarate** supplementation may improve recovery

after trauma.

CT Check Tags: Human; Support, Non-U.S. Gov't
 Cholecystectomy
 Drug Evaluation
 ***Glutamine: ME, metabolism**
 Ketoglutaric Acids: AD, administration & dosage
 *Ketoglutaric Acids: PD, pharmacology
 *Muscle Proteins: ME, metabolism
 *Nitrogen: UR, urine
 *Parenteral. . .

RN **328-50-7 (alpha-ketoglutaric acid); 56-85-9 (Glutamine)** ; 7727-37-9 (Nitrogen)

AN 90190142 MEDLINE

DN 90190142

TI **Alpha-ketoglutarate** and postoperative muscle catabolism.

AU Wernerman J; Hammarqvist F; Vinnars E

CS Department of Anaesthesiology and Intensive Care, St Goran's Hospital, Karolinska Institute, Stockholm, Sweden.

SO LANCET, (1990 Mar 24) 335 (8691) 701-3.
 Journal code: L0S. ISSN: 0140-6736.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199006

L16 ANSWER 5 OF 7 MEDLINE

AB After surgical trauma, protein synthesis, as well as the concentration of free **glutamine** in muscle, decreases. Total parenteral nutrition (TPN) alone does not prevent the decrease of **glutamine** in muscle, but TPN supplemented with **glutamine** or its precursor, **alpha-ketoglutarate**, maintains amino acid concentration in muscle and preserves protein synthesis. The aim of this study was to characterize a human trauma model using patients undergoing total hip replacement, and furthermore to investigate whether **glutamine** or **alpha-ketoglutarate** alone without TPN can prevent the postoperative decrease in muscle free **glutamine**. Metabolically healthy patients undergoing total hip replacement were randomized into three groups. The control group (n = 13) received glucose 2 g/kg body weight (BW) during **surgery** and the first 24 postoperative hours. The **glutamine** group (n = 10) received glucose 2 g/kg BW and **glutamine** 0.28 g/kg BW, and the **alpha-ketoglutarate** group (n = 10) received glucose 2 g/kg BW and **alpha-ketoglutarate** 0.28 g/kg BW. Muscle biopsies were performed before **surgery** and 24 hours postoperatively. Free **glutamine** concentration in muscle decreased from 11.62 +/- 0.67 to 9.80 +/- 0.36 mmol/kg wet weight in the control group ($P < .01$), whereas it remained unchanged in both the **glutamine** group and **alpha-ketoglutarate** group. Protein synthesis, as reflected by the concentration of total ribosomes, decreased significantly in the control group, but not in **glutamine** and **alpha-ketoglutarate** groups. Polyribosome concentration decreased significantly in both the control and **alpha-ketoglutarate** groups. Total hip replacement can be used as a reproducible trauma model, with characteristic changes in the muscle amino acid pattern and protein synthesis 24 hours postoperatively.(ABSTRACT TRUNCATED AT 250 WORDS)

L16 ANSWER 6 OF 7 MEDLINE

AB Serving as a reproducible human trauma model, patients (n = 21) undergoing elective cholecystectomy received postoperative total parenteral nutrition with (n = 9) or without (n = 12) **alpha-ketoglutarate** (AKG) supplementation. Skeletal muscle biopsy specimens were taken before **surgery** and on the third postoperative day. The postoperative decreases in the concentrations of free **glutamine** and basic amino acids seen in the control group were counteracted in the AKG group (p less than 0.05). Muscle protein synthesis was estimated by ribosome analysis. On the third postoperative day the control group showed a decline in the polyribosome concentration (25.8% +/- 4.5%; p less than 0.001). No significant change was observed in the AKG group. On each postoperative day the nitrogen balance was negative in the control group but not in the AKG group. In the control group the cumulative nitrogen balance amounted to -9.9 +/- 1.8 gm of nitrogen and in the AKG group -2.6 +/- 2.6 gm of nitrogen, which was significantly different (p less than 0.05). Administration of AKG, the carbon skeleton corresponding to **glutamine**, produced results similar to those seen when **glutamine** is added to postoperative total parental nutrition. The results suggest that the availability of precursors for **glutamine** synthesis in skeletal muscle is crucial for the degree of muscle **protein catabolism** after surgical trauma.

L16 ANSWER 7 OF 7 MEDLINE

AB The hypothesis that muscle **protein catabolism** after trauma is associated with a shortage of **alpha-ketoglutarate**, rather than **glutamine**, was tested. Addition of **alpha-ketoglutarate** to postoperative total parenteral nutrition prevented the decrease in muscle protein synthesis and free **glutamine** that usually occurs after **surgery**. **alpha-ketoglutarate** supplementation may improve recovery after trauma.

L22 ANSWER 2 OF 6 USPATFULL
PI US 5719119 19980217 <--
AB Parenteral nutrition aqueous solutions are provided which preferably contain **glutamine** together with other organic nitrogen containing compounds. The respective concentrations of the compounds present in any given such solution are. . .

SUMM . . . dissimilar clinically from the weakness complained of by patients receiving parenteral nutrition. It is not unreasonable to expect that elevated **muscle** Ca.sup.2+ plays a role in the functional myopathy seen in both of these clinical situations.

SUMM . . . plasma concentrations of free amino acids. Certain classes of amino acids are even missing, particularly the major plasma amino acid, **glutamine**, which is essential to the function of many organs, such as kidney and gut. It is further known that the. . .

SUMM Finally, the hormonal balance in many patients receiving such treatments favors the breakdown of protein with concurrent loss of **muscle** and tissue mass and the synthesis of glucose and urea. The action of hormones cab be effected by control of. . .

SUMM . . . 0.1 to 150 mM/L of at least one cation selected from the group consisting of sodium, potassium, calcium, magnesium, and **ammonium**.

SUMM Optionally, a composition from the class above described may additionally contain dissolved therein **glutamine**. Preferably, the quantity of **glutamine** employed in any given such composition is as herein below described.

SUMM The **glutamine** containing compositions of the present invention are applicable for use in various particular parenteral fluid therapy applications. The concentrations and the relationship of the component concentrations to one another in such application can be varied. In use, a **glutamine** containing composition may result in an increase in organ protein content and/or an increase in organ functional capacity compared to. . .

SUMM . . . redox action carboxylic acid near equilibrium couples which are suitable for use in parenteral nutrition therapy to restore and maintain **muscle** and other cellular functions.

SUMM . . . CoA, and urea, is a normal consequence of starvation or malnutrition. This process, called negative nitrogen balance, is accelerated by **trauma**, burns or wounds, infections and malignancy, and by **surgery**. It is recognized that the morbidity and mortality associated with **surgery** or cancer chemotherapy can be decreased if seriously ill patients can be returned toward a nutritionally normal state prior to **surgery**, or can be maintained in such a state while in the postoperative period or while undergoing a chemotherapy. Currently, therefore,. . . protein is impaired by obstruction, inflammatory disease or complications of antineoplastic therapy; (3) bowel rest is needed because of GI **surgery** or its complications, such as ileus, fistulae or anastomotic leaks; or (5) burns, **trauma**, infections, or other such so called hypermetabolic states exist.

SUMM . . . control in mitochondria, pp. 329-384, Adriatica Editrica, Bari, 1969). Thus, the concentration of the central amino acid transaminase pairs, namely **alpha ketoglutarate** x glutamate, and oxaloacetate x aspartate, or pyruvate x alanine, as well as the

ketoacids of the branched chain amino. . .

SUMM . . . so as to best achieve the result desired in a particular situation. Thus, in most clinical conditions, such as following **trauma**, burns or **surgery**, the hormonal status of the patient favors the catabolism of protein and the making of glucose. While the prevention of. . .

SUMM . . . acid composition of each of the blood, plasma, and extracellular fluid is tightly controlled by the liver, interacting with the **muscles** and the gut. Depending upon the tissue in question, gradients of from one to almost 100 fold in amino acid. . .

SUMM . . . were hydrolyzed completely in 1 liter of intracellular water, since 1 mM is about the concentration of this protein in **muscle** .

SUMM . . . the observed physiological myopathy, or inhibit the action of catabolic hormones which are usually present in excess in situations of **trauma**, malignancy, or simply malnutrition itself. The provision of adequate glucose to maintain cerebral function at all costs is an evolutionary. . .

SUMM . . . 4.97 93.8 22

4 1-Asparagine
132 0.02 ND 12
5 1-Cysteine
121 0.24 0.034 6
6 1-Glutamate.sup.-
147 0.031
0.158
9.19 58.2 28
7 1-**Glutamine**
146 0.300
ND 9.18 11
8 Glycine 75 0.124
0.370
5.09 13.7 28
9 1-Histidine
155 0.051
0.092
0.836
9.1 9
10 1-Proline
. . .

SUMM . . . gradients from 5 to 100 between perfusing fluid and liver. The same large concentration gradients occur in the case of **glutamine**. In general, the major traffic in nitrogen between the various organs is borne by alanine, **glutamine**, and the branched chain amino acids, leucine, isoleucine and valine.

SUMM In **trauma** (Kinney J M. The metabolic response of injury. in Nutritional aspects of care in the critically ill, Richards J R,. . . released amino acids to glucose, ketone bodies, and urea. The result is that the patient shows negative nitrogen balance and **muscle** wasting. Attempts have been made using so called parenteral nutrition solutions of amino acids to reverse this degradation of **muscle** and other organ mass. Unfortunately, using conventional forms of parenteral amino acid formulations, no significant gain in **muscle** nitrogen can be seen in the first weeks or months of therapy (Yeung C K et al. Effect of an. . .

SUMM Thus, normal plasma contains concentrations of [**ammonium** .sup.+, also characterized herein as NH.sub.4.sup.+].times.[alphaketoglutarate.sup.2-]/[glutamate.sup.-] the product of which is equivalent to the estimated mitochondrial free [NAD.sup.+. . .

SUMM Another example is the use of various ratios, around the physiologically normal, of [ketoglutarate]/[**glutamine**] which avoid the use of free ammonia, but which generate the ammonia and the production of intracellular glutamate.

SUMM TABLE 4

Couple	Ratio Range
[1-Lactate.sup.-]/	
	2:1 to 25:1
[1-Alanine]	
[1- **glutamine**]/	2:1 to 50:1
[**alpha ketoglutarate**.sup.2-]	
[1-glutamate.sup.1-]	
	1 .times. 10.sup.+3 - 100 .times. 10.sup.+3 Molar
[NH.sub.4.sup.+] [**alpha ketoglutarate**.sup.2-]	

SUMM . . . couples is optionally employed in a solution of this invention whether or not other nitrogen containing compounds are present (including **glutamine**) when control of the redox state is desired. Other nitrogen containing components present in normal plasma optionally may also be. . . available commercial formulations evaluated, for example, using rats with implanted venous cannulae, both before and after the induction of surgical **trauma**, demonstrate substantially improved capacity to control the redox state.

SUMM . . . 1). Thus, as shown in Tables 1 and 3, the order of decreasing concentration in normal plasma is roughly: 1 **glutamine**, 2 cysteine, 3 alanine, 4 valine, 5 glycine, 6 lysine.sup.+, 7 proline, 8 threonine, 9 serine, 10 leucine, 11 methionine,. . .

SUMM TABLE 5

Decreasing Concentration of Organic Nitrogen Materials in Normal Human Plasma

I.D. No.	Material
1	1-**glutamine**
2	1-cysteine
3	1-alanine
4	1-valine
5	glycine
6	1-lysine
7	1-proline
8	1-threonine
9	1-serine
10	1-leucine
11	1-methionine
12	1-tryptophane
13	1-histidine
14	1-arginine
15	1-isoleucine
16	1-glutamate
17	1-tyrosine
18	1-phenylalanine
19	1-asparagine
20	1-aspartate

SUMM . . . phenylalanine, 14 isoleucine, 6 proline, 7 threonine, 12 histidine, 13 tryptophane, 14 tyrosine, with the major amino acid in plasma, 1-**glutamine** being omitted altogether, as are the important redox active amino acids, 15 glutamate.sup.- and 19 aspartate.sup.-, and also, inexplicably, 8. . .

SUMM . . . tissue concentrations of many amino acids are related to one another through the concentration of common ketoacids, particularly pyruvate and **alpha ketoglutarate** (see Veech R L and Krebs H A, in The energy level and metabolic control in mitochondria, pp. 329-382, Adriatica. . . Biol Chem 254:6538-6547, 1979). It would, therefore, seem reasonable that, during the administration of parenteral nutrition, supplements aimed at restoring **muscle** function and

increasing in protein mass, some consideration be given to control the natural order of metabolite levels, in addition. . . more to the point, the prior art parenteral amino acid supplements do not lead to an increased functional capacity in **muscle** which is desired to decrease operative mortality and morbidity in a reasonable pre-operative period of supplementation. Unlike the feeding of. . .

SUMM . . . addition to the abnormalities in calcium and pyrophosphate metabolism discussed earlier. It has been suggested that the persistence of the **muscle** weakness and the failure of **muscle** mass to increase in patients receiving conventionally formulated parenteral amino acid supplements may, in fact, be a myopathy secondary to increased intracellular calcium content (see Russell D. et al. Nitrogen versus **muscle** calcium in the genesis of abnormal **muscle** function in malnutrition. J Paren Ent Nutr 9:415-421, 1985).

SUMM . . . of aqueous solutions adaptable for use in human parenteral nutrition therapy. A solution of this class tends (a) to normalize **muscle** and other organ function, (b) to maintain normal cellular phosphorylation potential, and (c) avoid acidosis and bone pain characteristic of. . .

SUMM As indicated above, compositions of this invention preferably contain **glutamine**. A **glutamine**-containing such composition (solution) preferably contains from about 0.03 to 120 millimoles per liter of **glutamine** plus at least one metabolizable nitrogen containing compound selected from among those shown in the Table 7 listing below. In. . . a preferred solution of this invention is determined by a constant K which interrelates concentration ratios shown in Table 6 **glutamine** concentration with (other) amino acid concentration as shown by the following formula:

SUMM K=**glutamine** concentration/nitrogen containing compound concentration

SUMM . . . this invention also contains at least one inorganic cation selected from the group consisting of sodium, potassium, calcium, magnesium and **ammonium**. The total quantity of such metabolic cation(s) present in a given solution ranges from about 0.1 to 150 mM/l.

Each such dissolved metabolized organic nitrogen containing compound (including **glutamine**), when present in a solution of this invention, is preferably present in a concentration range extending from about 1 to. . .

DETD

Amino Acid	mM/L
1-**glutamine**	30.0
1-cysteine	24.0
1-alanine	14.0
1-valine	14.0
glycine	12.0
1-lysine	11.0
1-proline	11.0
1-threonine	9.0
1-serine	8.0

1-leucine
8.0

DETD . . . Nitrogen Containing Parenteral Nutrition Solutions
Concentrations are in mMoles/L

	Normal Plasma	Example 1.1 200 .times. Normal Plasma	Example 1.2 150 .times. Normal Plasma
1-**glutamine**	0.30	60	45
Group I			
1-cysteine	0.24	48	36
Group II			
1-alanine	0.14	28	21
1-valine	0.14	27	20
glycine	0.12	25	19
1-lysine.sup.+	0.11	21	16
1-proline. . .			

DETD . . . Containing Parenteral Nutrition Solutions
Concentrations are in mMoles/L.

	Example 1.3 200 .times. Normal	Example 1.4 200 .times. Normal	Example 1.5 200 .times. Normal
1-**glutamine**	60	60	60
Group I			
1-cysteine	48	48	48
Group II			
1-alanine	28	28	28
1-valine	27	27	27
glycine	25	25	25
1-lysine.sup.+	21	21	21
1-proline. . .			

DETD . . . 1984. In chronic experiments, change in lean body and bone mass is measured. Exercise tolerance and .sup.31 NMR of their **muscles** at rest, and during exercise, is measured, and the animals are sacrificed. The accumulation of pyrophosphate, phosphate, calcium, and other relevant electrolytes and metabolic intermediates is determined in blood, liver and skeletal **muscle** after freeze clamping of these organs during administration of the two different parenteral nutrition formulations. In addition, the total protein content of liver and skeletal **muscle** on the two types of formulations is determined as is the liver, **muscle** and blood content of amino acids, soluble CoA's, phosphorylation potential or [ATP]/[ADP][Pi] ratio, the redox state of the free pyridine. . . hind limb placed in a NMR tube and pulsed by electrical stimulation. It is found that the function of skeletal **muscle** with the new formulations is approximately normal.

CLM What is claimed is:
. . . dissolved therein: (A) from about 1 to 150 mMoles/L of at least one

of the following metabolizable nitrogen containing compounds: l-**glutamine** l-cysteine l-alanine l-valine glycine l-lysine.sup.+ l-proline l-threonine l-serine l-leucine l-tryptophane l-histidine **ammonium**.sup.+ l-carnitine l-arginine.sup.+ l-isoleucine l-ornithine l-glutamate.sup.- l-methionine l-tyrosine l-phenylalanine l-aspartate.sup.- l-asparagine l-citrulline but always containing l-**glutamine** the total quantity of all such compound(s) in any given such solution being not more than about 1000 mMoles/Liter, (B).

. of at least one carboxylate anion selected from the group consisting of l-lactate with substantially no d-lactate, pyruvate, d-betahydroxybutyrate, acetoacetate, **alpha Ketoglutarate** l-glutamate, and bicarbonate, and (C) from about 0.1 to 150 mMoles/Liter of at least one cation selected from the group consisting of sodium, potassium, calcium, magnesium, and **ammonium**.

. . . . of claim 1 wherein said nitrogen containing compounds include at least one material selected from the group consisting of alanine, **glutamine**, glutamate, wherein said carboxylate anions include at least one selected from the group consisting of l-lactate and **alpha ketoglutarate**, and wherein: (A) from 1 to 150 mMoles/Liter total of l-lactate anions and alanine are present in a ratio in. . . liter of l-lactate anions to alanine ranges from about 0.5:1 to 20:1, (B) from 1 to 150 mMoles/Liter total of **glutamine** and **alpha ketoglutarate** anions are present, the ratio in moles per liter of **glutamine** to alphaketoglutarate anions ranges from about 1:1 to 50:1, and (C) from about 1 to 150 mMoles/Liter total of when **ammonium** and glutamate and **alpha ketoglutarate** anions are present, the ratio in moles/liter of [glutamate.sup.-] to the product of moles/liter **ammonium**.sup.+ times moles/liter of **alpha ketoglutarate**.sup.2- ranges from about 1000 to 100,000 Moles/Liter.

5. An aqueous solution adaptable for use in human parenteral nutrition therapy and which solution tends (a) to normalize **muscle** and other organ function and (b) to maintain normal cellular phosphorylation potential, said solution comprising from about 0.03 to 120 millimoles per liter of **glutamine** plus at least five metabolizable nitrogen containing compounds selected from among the following compounds:

Class No.	Metabolizing Nitrogen Containing Compound
I	1-Cysteine
II	1-Alanine
	1-Valine
	Glycine
	1-Lysine.sup.+
	1-Proline
III	1-Threonine
	1-Serine
	1-Leucine
	1-Tryptophane
	1-Histidine
	ammonium.sup.+
	1-Carnitine
IV	1-Arginine
	1-Isoleucine
	1-Ornithine
	1-Glutamate.sup.-
	1-Methionine
	1-Tyrosine
	1-Phenylalanine

1-Taurine
1-Aspartate
1-Asparagine
1-Citrulline
1-Aminobutyrate

---

the concentration range of each such compound in millimoles per liter being determined by the following formula: ##EQU2## where the **glutamine** concentration is in millimoles per liter and the value of K for each given such nitrogen containing compound is determined. . .

. . . solution of claim 5 additionally containing at least one cation selected from the group consisting of sodium.sup.+, potassium.sup.+, magnesium.sup.2+, calcium.sup.+, **ammonium**.sup.+ and at least one anion selected from the group consisting of l-lactate.sup.- with substantially no d-lactate, pyruvate.sup.-, d-betahydroxybutyrate.sup.-, acetoacetate.sup.-, and. . .

. . . acid, acetoacetic acid and alphaketoglutaric acid with at least one metabolizable nitrogen containing compound selected from the group consisting of l-**glutamine** l-cysteine l-alanine l-valine glycine l-lysine.sup.+ l-proline l-threonine l-serine l-leucine l-tryptophane l-histidine **ammonium** .sup.+ l-carnitine l-arginine.sup.+ l-isoleucine l-ornithine l-glutamate.sup.- l-methionine l-tyrosine l-phenylalanine l-aspartate.sup.- l-asparagine l-citrulline.

. . . dissolved therein: (A) from about 1 to 150 mMoles/L of at least one of the following metabolizable nitrogen containing compounds: l-**glutamine** l-cysteine l-alanine l-valine glycine l-lysine.sup.+ l-proline l-threonine l-serine l-leucine l-tryptophane l-histidine **ammonium**.sup.+ l-carmotome l-arginine.sup.+ l-isoleucine l-ornithine l-glutamate l-methionine l-tyrosine l-phenylalanine l-aspartate.sup.- l-asparagine l-citrulline but always containing l-**glutamine** the total quantity of all such compound(s) in any given such solution being not more than about 1000 mMoles/Liter, (B). . .

. 0.1 to 150 mMoles/Liter of at least one cation selected from the group consisting of sodium, potassium, calcium, magnesium, and **ammonium**.

. . . dissolved therein: (A) from about 1 to 150 mMoles/L of at least one of the following metabolizable nitrogen containing compounds: l-**glutamine** l-cysteine l-alanine glycine l-lysine.sup.+ l-proline l-threonine l-serine l-leucine l-tryptophane l-histidine **ammonium**.sup.+ l-carmotome l-arginine+ l-isoleucine l-ornithine l-glutamate.sup.- l-methionine l-tyrosine l-phenylalanine l-aspartate.sup.- l-asparagine l-citrulline but always containing L-**glutamine** the total quantity of all such compound(s) in any given such solution being not more than about 1000 mMoles/Liter, (B). . .

. 0.1 to 150 mMoles/Liter of at least one cation selected from the group consisting of sodium, potassium, calcium, magnesium, and **ammonium**, wherein said nitrogen containing compounds include at least one material selected from the group consisting of alanine, **glutamine**, glutamate, wherein said carboxylate anions include at least one selected from the group consisting of l-lactate and **alpha ketoglutarate**, and wherein: (A) from 1 to 150 mMoles/Liter total of l-lactate anions and alanine are present in a ratio in. . . liter of l-lactate anions to alanine ranges from about 0.5:1 to 20:1, (B) from 1 to 150 mMoles/Liter total of **glutamine** and **alpha ketoglutarate** anions are present, the ratio in moles per liter of **glutamine** to alphaketoglutarate anions ranges from about 1:1 to 50:1, and (C) from about 1 to 150 mMoles/Liter total of when **ammonium** and glutamate and **alpha ketoglutarate** anions are present, the ratio in

moles/liter of glutamate- to the product of moles/liter **ammonium** .sup.+ times moles/liter of **alpha ketoglutarate** .sup.2- ranges from about 1000 to 100,000 Moles/Liter.

AN 1998:17284 USPATFULL|
TI Parenteral nutrition therapy with amino acids|
IN Veech, Richard L., Rockville, MD, United States
PA British Technology Group, Ltd., London, England (non-U.S. corporation)
PI US 5719119 19980217 <--
AI US 1993-53291 19930426 (8)
RLI Continuation of Ser. No. US 1991-782751, filed on 21 Oct 1991, now abandoned which is a continuation of Ser. No. US 1990-479237, filed on 12 Feb 1990, now abandoned which is a continuation of Ser. No. US 1986-940332, filed on 17 Dec 1986 which is a continuation-in-part of Ser. No. US 1985-810916, filed on 18 Dec 1985, now abandoned
DT Utility|
EXNAM Primary Examiner: Weddington, Kevin E.|
LREP Hill, Steadman & Simpson|
CLMN Number of Claims: 14|
ECL Exemplary Claim: 1|
DRWN No Drawings
LN.CNT 1246|
CAS IND

AB Parenteral nutrition aqueous solutions are provided which preferably contain **glutamine** together with other organic nitrogen containing compounds. The respective concentrations of the compounds present in any given such solution are typically approximately multiples of the concentration of the same compounds as found in normal human plasma, and the respective mole ratios of various such compounds in any given such solution relative to one another are approximately the same mole ratio associated with the same compounds as found in normal human plasma. Processes for using such solutions are provided.

L14 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2001 ACS

TI **Glutamine** synthetase and glutamate synthase activities in high **ammonium** grown wheat cells

SO Phytochemistry (**1993**), 34(3), 637-44
CODEN: PYTCAS; ISSN: 0031-9422

AB . . . cultures of wheat (Triticum aestivum L. cv Heines Koga II) were grown on media contg. various amts. of nitrate and **ammonium**. Increasing the external **ammonium** concn. from 2 to 25 mM led to a 200% increase in the specific NADH-dependent glutamate synthase activity. In contrast, the specific **glutamine** synthetase activity decreased by 80%. High **ammonium** grown cells exhibited a two-10-fold elevation of **glutamine**, asparagine, alanine and **ammonium**, but up to an 80% decrease in malate, **.alpha.-ketoglutarate**, and nitrate pools. Cells exclusively supplied with **ammonium** nitrogen (nitrate starvation) ceased sol. **protein** synthesis and showed a specific increase in glutamate dehydrogenase activity. Regardless of changes in the nitrogen supply, the in vitro measured activity of NADH-dependent glutamate synthase was similar to the calcd. in vivo rate of **ammonium** assimilation. The in vitro measured activity of **glutamine** synthetase was neg. related to the rate of **ammonium** assimilation, while the product of the in vitro measured activity of **glutamine** synthetase and the cellular concn. of **ammonium** was pos. related to it. The results are discussed in terms of an in vivo regulation of **glutamine** synthetase activity by **glutamine**, **.alpha.-ketoglutarate** and the cytosolic concn. of **ammonium**.

ST wheat **glutamine** synthetase glutamate synthase **ammonium**

IT Translation, genetic
(by wheat cells, under **ammonium** excess)

IT Wheat
(**glutamine** synthetase and glutamate synthase of, under **ammonium** excess)

IT Amino acids, biological studies
RL: BIOL (Biological study)
(of wheat cells, under **ammonium** excess)

IT Plant stress
(**ammonium** excess, wheat **glutamine** synthetase and glutamate synthase under)

IT Plant nutrition
(disorder, of nitrogen assimilation, in wheat cells under **ammonium** excess)

IT Plant stress
(nitrate deficiency, wheat **glutamine** synthetase and glutamate synthase under **ammonium** excess and)

IT Plant tissue culture
(suspension, heterotrophic, of wheat cells, **glutamine** synthetase and glutamate synthase of, under **ammonium** excess)

IT 7727-37-9, Nitrogen, biological studies
RL: BIOL (Biological study)
(assimilation of, by wheat cells under **ammonium** excess)

IT 56-41-7, Alanine, biological studies 56-85-9, **Glutamine**, biological studies 70-47-3, Asparagine, biological studies 328-50-7, **.alpha.-Ketoglutaric acid** 6915-15-7, Malic acid 9023-70-5, **Glutamine** synthetase 65589-88-0, Glutamate synthase
RL: BIOL (Biological study)
(of wheat cells, under **ammonium** excess)

IT 7727-37-9
RL: BIOL (Biological study)
(plant nutrition, disorder, of nitrogen assimilation, in wheat cells

under **ammonium** excess)

IT 14797-55-8, Nitrate, biological studies
RL: BIOL (Biological study)
(wheat **glutamine** synthetase and glutamate synthase under **ammonium** excess and deficiency of)

IT 14798-03-9, **Ammonium**, biological studies
RL: BIOL (Biological study)
(wheat **glutamine** synthetase and glutamate synthase under excess of)

AN 1994:27545 CAPLUS
DN 120:27545
TI **Glutamine** synthetase and glutamate synthase activities in high **ammonium** grown wheat cells
AU Fricke, Wieland
CS Inst. Pflanzenphysiol., Justus-Liebig-Univ., Giessen, D-6300, Germany
SO Phytochemistry (**1993**), 34(3), 637-44
CODEN: PYTCAS; ISSN: 0031-9422
DT Journal
LA English

L14 ANSWER 9 OF 12 USPATFULL
AN 97:56535 USPATFULL
TI Process for producing an optically active .gamma.-hydroxy-L-glutamic acid
IN Katsumata, Ryoichi, Machida, Japan
Hashimoto, Shinichi, Machida, Japan
PA Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan (non-U.S. corporation)
PI US 5643769 19970701 <--
AI US 1995-501177 19950711 (8)
PRAI JP 1994-158656 19940711
DT Utility
EXNAM Primary Examiner: Lilling, Herbert J.
LREP Antonelli, Terry, Stout & Kraus, LLP
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1306
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5643769 19970701 <--
SUMM An optically active .gamma.-hydroxy-L-glutamic acid is known to have activity of inhibiting **glutamine** synthetase [Khim-Farm. Zh., 18, 655 (1984)] or incorporation of glutamic acid by presynaptic vesicle [Neurochem. Res., 18, 79 (1993)], and. . .
DETD Particularly, a mutant in which at least one of .**alpha**.-**ketoglutaric acid** dehydrogenase activity and optically active 4-hydroxy-2-ketoglutaric acid degrading activity is deleted or decreased compared to its parent strain can be. . .
DETD . . . onto a suitable agar plate medium, obtaining the grown mutant, and selecting a strain in which at least one of .**alpha**.-**ketoglutaric acid** dehydrogenase activity and optically active 4-hydroxy-2-ketoglutaric acid degrading activity is deleted or decreased compared to its parent strain.
DETD Specific examples of the mutant include Escherichia coli HKK2 (sucA, iclR, trp) which lacks .**alpha**.-**ketoglutaric acid** dehydrogenase activity and Escherichia coli HKK27 which lacks .**alpha**.-**ketoglutaric acid** dehydrogenase activity and decreases L-4-hydroxy-2-ketoglutaric acid degrading activity. Escherichia coli HKK27 strain was deposited with the National Institute of Bioscience. . .
DETD . . . Escherichia Coli HKK27/pHK10 is an example of a strain which has both of the mutations, that is, the lack of .**alpha**.-**ketoglutaric acid** dehydrogenase and the decrease in L-4-hydroxy-2-ketoglutaric acid degrading activity and which has increased glutamic acid dehydrogenase activity. Escherichia Coli HKK27/pHK10. . .
DETD . . . be employed so long as it can be assimilated by the microorganism used. Examples of the nitrogen source include ammonia, **ammonium** salts of inorganic and organic acids such as **ammonium** sulfate, **ammonium chloride**, **ammonium** acetate and **ammonium** phosphate, other nitrogen-containing compounds, peptone, meat extract, yeast extract, corn steep liquor, casein hydrolysates, soybean cakes, soybean cake hydrolysates, fermented. . .
DETD . . . it can be assimilated by the microorganism used. Examples of the inorganic salts include potassium dihydrogen phosphate, dipotassium hydrogen phosphate, **ammonium** sulfate, **ammonium chloride**, sodium chloride, magnesium sulfate, ferrous sulfate and manganese sulfate. Trace elements such as calcium, zinc, boron,

copper, cobalt and molybdenum. . .
DETD . . . II include a dried cells, lyophilized cells, surfactant- or organic solvent-treated cells, enzymatically-treated cells, ultrasonically-treated cells, mechanically compressed cells, cellular **protein** fractions, and immobilized product of unprocessed cells or processed cells.
DETD In processes I and II of the present invention, the amino group donor used includes ammonia, inorganic **ammonium** salts such as **ammonium** sulfate, **ammonium chloride** and urea, and amino acids such as aspartic acid. The concentration of the amino group donor is 0.1 to 100. . .
DETD . . . -

8. Utilization of citric acid
   Koser's method +
   Christensen's method +
9. Utilization of inorganic nitrogen source
   Nitrates +
   Ammonium salts +
10. Pigment production
   King A medium -
   King B medium -
11. Urease +
12. Oxidase -
13. Catalase +
14. Growth range

. . .
DETD . . . can be employed so long as it can be assimilated by the microorganism. Examples of the nitrogen source include ammonia, **ammonium** salts of inorganic and organic acids such as **ammonium** sulfate, **ammonium chloride**, **ammonium** acetate and **ammonium** phosphate, other nitrogen-containing compounds, peptone, meat extract, yeast extract, corn steep liquor, casein hydrolysates, soybean cake, soybean cake hydrolysates, fermented. . .
DETD . . . it can be assimilated by the microorganism used. Examples of the inorganic salt include potassium dihydrogen phosphate, dipotassium hydrogen phosphate, **ammonium** sulfate, **ammonium chloride**, sodium chloride, magnesium sulfate, ferrous sulfate and manganese sulfate. In addition, trace elements such as calcium, zinc, boron, copper, cobalt. . .
DETD . . . biocatalyst III include a dried cells, lyophilized cells, surfactant- or organic solvent-treated cells, enzymatically-treated cells, ultrasonically-treated cells, mechanically-compressed cells, cellular **protein** fraction, and immobilized product of unprocessed cells or processed cells.
DETD . . . coli ATCC 33625, which is a sub-strain of E. coli K-12, and E. coli HKK2 (sucA, iclR, trp) deprived of **.alpha.-ketoglutaric acid** dehydrogenase activity were cultured in a test tube filled with 3 ml of L medium overnight at 37.degree. C. Two. . . of sterilized 1M MgSO.sub.4 and 0.1 ml of sterilized 1M CaCl.sub.2] further containing 0.4% glucose, 0.05% succinic acid, 0.2% **ammonium** sulfate, 100 mg/liter of L-tryptophan, 0.1% yeast extract and 0.1% peptone, and cultivated at 37.degree. C. for 8 hours. The. . .
DETD . . . of E. coli strain was added thereto in an amount of 80 .mu.l each. Further, 40 .mu.l of a 20% **ammonium** sulfate solution, 48 .mu.l of a 50% glucose solution and 80 .mu.l of M9C solution (a solution containing 60 g. . .
DETD A mutant having decreased L-4-hydroxy-2-ketoglutaric acid degrading activity was derived from **.alpha.-ketoglutaric acid** dehydrogenase activity-deficient mutant E. coli HKK2 (sucA, iclR, trp) of E. coli K-12. E. coli HKK2 was cultivated in L. . . the mixture was selected as the strain having decreased L-4-hydroxy-2-

ketoglutaric acid degrading activity. Thus, E. coli HKK27 having deficiency of **.alpha.-ketoglutaric acid** hydrogenase activity and decreased L-4-hydroxy-2-ketoglutaric acid degrading activity was obtained. The strain having deficiency of . **alpha.-ketoglutaric acid** hydrogenase activity and decreased L-4-hydroxy-2-ketoglutaric acid degrading activity can be also obtained by deriving the mutant having decreased D-4-hydroxy-2-ketoglutaric acid. . .

DETD . . . strain suspension prepared above was added thereto in an amount of 80 .mu.l each. Further, 40 .mu.l of a 20% **ammonium** sulfate solution, 48 .mu.l of a 50% glucose solution and 80 .mu.l of M9C solution were added to each of. . .

DETD . . . centrifuged to obtain a supernatant. To 0.4 ml of the supernatant were added a suspension of E. coli HKK27/pHK10, glucose, **ammonium** sulfate and M9C solution as in Example 6. The total amount of the mixture was adjusted to 0.8 ml with. . .

DETD . . . (0.5 ml) having the composition mentioned below, 0.5 ml of a 50% glucose solution and 1 ml of a 10% **ammonium chloride** solution were sterilized and added to each of the test tubes. Further, 0.5 ml of a culture of Arthrobacter protophomiae. . .

DETD . . . added to a 2-liter conical flask containing 750 ml of M9 medium supplemented with 0.4% glucose, 0.05% succinic acid, 0.2% **ammonium** sulfate, 100 mg/liter L-tryptophan, 0.1% yeast extract, 0.1% peptone and 10 mg/liter tetracycline, and the mixture was cultivated at 37.degree.. . .

DETD . . . milliliter of the above-obtained E. coli HKK27/pHK10 suspension, 4.8 ml of a 50% glucose solution, 4 ml of a 20% **ammonium** sulfate solution, 8 ml of M9C solution and 5.2 ml of sterilized water were added to 50 ml of the. . .

DETD E. coli ATCC 33625 derived from E. coli K-12 and mutant E- coli HKK2 (sucA, iclR, trp) deprived of **.alpha.-ketoglutaric acid** dehydrogenase activity were cultivated in a test tube containing 3 ml of L medium overnight at 37.degree. C. Two milliliter. . . to a 300-milliliter conical flask filled with 50 ml of M9 medium supplemented with 0.4% glucose, 0.05% succinic acid, 0.2% **ammonium** sulfate, 100 mg/liter L-tryptophan, 0.1% yeast extract and 0.1% peptone, and the mixture was cultivated at 37.degree. C. for 8. . .

DETD . . . E. coli strain suspension was added thereto in an amount of 80 .mu.l each. Further, 40 .mu.l of a 20% **ammonium** sulfate solution, 48 .mu.l of a 50% glucose solution and 80 .mu.l of M9C solution were added to each of. . .

DETD . . . coli strain suspension was further added thereto in an amount of 80 .mu.l each. Moreover, 40 .mu.l of a 20% **ammonium** sulfate solution, 48 .mu.l of a 50% glucose solution and 80 .mu.l of M9C solution were added to each of. . .

DETD . . . mixture was centrifuged to obtain a supernatant. To 0.4 ml of the supernatant were added the HKK27/pHK10 strain suspension, glucose, **ammonium** sulfate and M9C solution in the same manner as in Example 13. The total amount of the mixture was adjusted. . .

DETD . . . MSC medium having the composition mentioned below, 0.5 ml of a 50% glucose solution and 1 ml of a 10% **ammonium chloride** solution were sterilized and added to each of the test tubes. Still further, 0.5 ml of a culture of Arthrobacter. . .

DETD . . . a 2-liter conical flask filled with 750 ml of M9 medium supplemented with 0.4% glucose, 0.05% of succinic acid, 0.2% **ammonium** sulfate, 100 mg/liter L-tryptophan, 0.1% yeast extract, 0.1% peptone and 10 mg/liter tetracycline. The mixture was cultivated at 37.degree. C.. . .

DETD . . . milliliter of the obtained E. coli HKK27/pHK10 suspension, 4.8 ml of a 50% glucose solution, 4 ml of a 20% **ammonium** sulfate solution, 8 ml of M9C solution and 5.2 ml of sterilized water were added

to 50 ml of the. . .

DETD . . . active .gamma.-hydroxy-L-glutamic acid advantageously on an industrial scale, the optically active .gamma.-hydroxy-L-glutamic acid being known to have activity of inhibiting **glutamine** synthetase activity or incorporation of glutamic acid by presynaptic vesicle and being useful as a reagent for investigation of the. . .

CLM What is claimed is:

. . . the compound capable of being converted into pyruvic acid by biocatalyst I is glucose, fructose, maltose, glycerol, lactic acid or **ammonium** lactate.

11. The process of claim 10 wherein the microorganism is a strain in which at least one of **.alpha.-ketoglutaric acid** dehydrogenase (**.alpha.-ketoglutarate** dehydrogenase) activity and optically active 4-hydroxy-2-ketoglutaric acid degrading activity is decreased or deleted.